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ANTIHYPERGLYCEMIC ACTIVITY AND NEPHROTOXICITY OF BIDARA (ZIZIPHUS MAURITIANA LAM.) LEAF ETHANOL EXTRACTS

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ABSTRACT

Bidara (Ziziphus mauritiana Lam.) leaves, as a native Indonesian plant, are often used in traditional medicine. As a traditional medicine, bidara (Z. mauritiana Lam.) leaves have the potential to be a source of medicine in the world of modern medicine. However, its safety as a medicinal product is still unknown. This study aims to determine the antihyperglycemic and acute toxicity effect of bidara (Z. mauritiana Lam.) leaf extract on the kidneys of Wistar strain (Rattus norvegicus) rats. This study involved 24 Wistar rats (Rattus norvegicus) that were induced with alloxan and received interventions in the form of administration of Na-CMC, metformin, or bidara (Z. mauritiana Lam.) leaf ethanol extract at dosages of 50, 150, 300, and 500 mg/kgBW, depending on the test animal group. This study found that the ethanol extract of bidara (Z. mauritiana Lam.) leaves has antihyperglycemic characteristics, as indicated by a decrease in blood glucose levels in test animals that received the ethanol extract of bidara (Z. mauritiana Lam.) leaves at dosages of 150 mg/kgBW ($p<0.01$), 300 mg/kgBW ($p<0.001$), and 500 mg/kgBW ($p<0.001$). In addition, at all doses administered, no significant differences were found in renal histopathology between experimental groups, nor in creatinine, urea, or glomerular filtration rate ($p>0.05$). It can be concluded that the ethanol extract of bidara (Z. mauritiana Lam.) leaves is not nephrotoxic up to a dose of 500 mg/kgBW.

Keywords: Ber., creatinine., kidney., urea.

INTRODUCTION

In Indonesian cultural diversity, traditional medicine is one form of cultural heritage that is still practiced today. Traditional medicine is a collection of knowledge, skills, and practices based on theories, beliefs, and/or experiences that are original and specific to a particular culture and are used as methods of prevention, diagnosis, improvement, and treatment of physical health by utilizing plants/animals that grow around the community.[1] Thus, traditional medicine is rooted in two main aspects: local plants/animals and local culture. This means a particular plant/animal can have different functions in traditional medicine in different cultures.

In Indonesia, traditional medicine generally comes from local plants from the surrounding environment and the forest. With its enormous biodiversity and many ethnic groups, Indonesia has many practices in using traditional medicine. One of the traditional medicines often used by Indonesians is Bidara (*Z. mauritiana* Lam.). Bidara, also known locally as widara, dara, bekul/bekol, or kalangga in various regions in Indonesia, or ber, Indian jujube, or Malay jujube internationally, is a plant that can grow as a shrub or tree with fruits commonly consumed as snacks. Most commonly, Bidara is used as a remedy for stomach aches and diarrhea, while in certain tribes, Bidara is also used as a cough remedy and burn remedy and is believed to help treat chronic diseases such as diabetes mellitus, heart disease, and others.[2–4] However, using Bidara as medicine is generally based only on empirical evidence and without scientific evidence. Therefore, various studies explore the benefits of Bidara in modern medicine by utilizing various parts of the Bidara plant, ranging from roots, bark, leaves, and fruit.[5–10] These studies not only attempt to explain the effects of Bidara on diseases generally treated with Bidara but also on chronic diseases such as diabetes mellitus, heart disease, and cancer.[5–12] However, the toxicity study is still limited in the context of Bidara.

Toxicity is an undesirable effect of chemical, biological, or physical agents on an organism.[13] The toxicity of an agent can occur through various mechanisms involving molecular, cellular, or biochemical processes that occur independently in isolation or within a complex mechanism.[14] Many toxic organisms are sources of therapeutic compounds in modern medicine, such as botulinum toxin (botox), castor bean extract (*Ricinus comunis*), and various other organisms.[15–17] Therefore, knowing the toxic effects of an agent is very important to ensure that the therapeutic benefits provided are more significant than the toxic effects of an agent.[18]

This study aims to determine the antihyperglycemic and nephrotoxicity of Bidara (*Z. mauritiana* Lam.) leaves ethanol extract on rats (*Rattus norvegicus*) of the Wistar strain.

METHODS

This study is a true experimental study with a post-test only with a control group design, which was conducted in April 2024 in a private research facility in Medan. This study uses rats (*Rattus norvegicus*) of the Wistar strain as experimental subjects. This study consists of six intervention groups (Table 1). The number of experimental subjects required for this study was calculated using the Federer formula, and it was found that a minimal sample of four per experiment group was required, with a total sample of 24 rats.

After the rats are procured, they are acclimatized in a pen made with a polyvinyl chloride (PVC) container box. After the acclimatization, the rats are grouped into six different groups, namely negative control, positive control, and four different dosages of bidara (*Z. mauritiana*) leaves ethanol extract (50, 150, 300, and 500 mg/kgBW). Each rat's blood glucose level was measured using a glucometer before being given different interventions. Blood was acquired from the tail using a lancet. After blood glucose level was acquired, each rat received alloxan intraperitoneally with the dosage of 130 mg/kgBW. The second blood glucose level was measured two hours after the induction of hyperglycemia using alloxan. Each group then received an intervention according to their group. After that, the blood glucose level was measured regularly every three days. On day 28th, the final blood glucose level was measured, followed by euthanasia using carbon dioxide according to American Veterinary Medical Association guidelines. Terminal blood collection was conducted by exsanguination using a syringe to the vena cava. After the exsanguination, the kidney was collected and refrigerated to prevent decomposition. The kidney then turned into a histology slide for histopathology study. Data in this study was analyzed using ANOVA.

Table 1 Experiment subjects grouping and respective intervention

Group	Intervention
Negative Control	Na-CMC
Positive Control	Metformin
BLEE 50	50 mg/kgBW of Bidara (Z. mauritiana) leaves ethanol extract
BLEE 150	150 mg/kgBW of Bidara (Z. mauritiana) leaves ethanol extract
BLEE 300	300 mg/kgBW of Bidara (Z. mauritiana) leaves ethanol extract
BLEE 500	500 mg/kgBW of Bidara (Z. mauritiana) leaves ethanol extract

This study and its protocols have been declared ethically appropriate by the Ethical Committee for Health Research of Prima Indonesia University by letter No. 021/KEPK/UNPRI/II/2024.

RESULTS

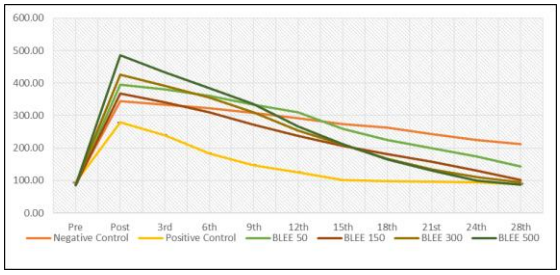

Figure 1 Graph of blood glucose level during the experiment (mg/dL)

This study found that two hours after the administration of alloxan (post-induction), all experiment subjects blood glucose levels spiked compared to the pre-induction level. Three days after administering the respective intervention, the blood glucose level decreased compared to the post-induction level across all groups, although the decrease is to the pre-induction level. The blood glucose level continuously dropped for every routine measurement (Figure 1).

Using ANOVA, it was found that there was a significant difference among all groups from the sixth day onwards ($p<0.05$), but there was no significant difference among all groups pre-induction, post-induction, and the third day ($p>0.05$). Hence, a post-hoc test was only required for the blood glucose level from the sixth day onward. Post-hoc test found a significant difference in blood glucose levels at the end of the experiment between the negative control group, positive control group, and all BLEE groups, except for BLEE 50 (0<0.001). However, a significant difference toward the negative control group appeared later in BLEE 150 (on the 24th day) ($p<0.05$), while the BLEE 300 and 500 difference appeared from the 21st day ($p<0.05$). Compared with the positive control group, there are no significant differences toward the BLEE 150, 300, and 500 from the 12th day ($p>0.05$).

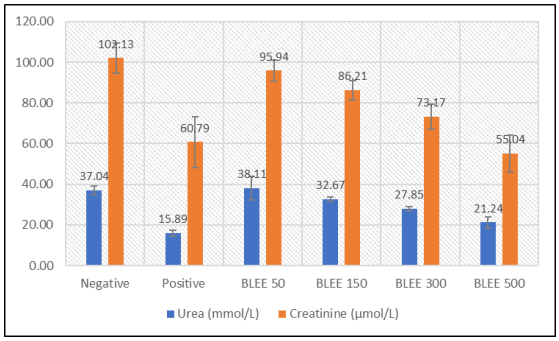

Figure 2 Comparison of serum urea (blue) and creatinine (orange) levels across the groups

Among all groups, the highest level of urea was found in the BLEE 50 (38.11 mmol/L; SD: 5.92 mmol/L), slightly higher than the negative control group (37.04 mmol/L; SD: 2.15 mmol/L). Meanwhile, the lowest serum urea level was found in the positive control group (15.89 mmol/L; SD: 1.38 mmol/L), followed by the BLEE 500 group (21.24 mmol/L; SD: 2.58 mmol/L).

Despite the data of serum levels of urea and creatinine being distributed normally ($p>0.05$), the homogeneity assumptions were not met ($p<0.05$). Hence, the analysis was conducted using Welch ANOVA. Analysis using Welch ANOVA found that there are significant differences among groups in serum levels of urea (F: 37.48, $p<0.001$) and creatinine (F: 22.69, $p<0.001$). Further post-hos test using Games-Howell found that these differences are not toward the nephrotoxicity but tend to be nephroprotective. There are significant differences between the negative control and the positive control ($p<0.001$), BLEE 300 ($p<0.01$), and 500 ($p<0.001$); however, there are no significant differences between the positive control and BLEE 500 ($p>0.05$).

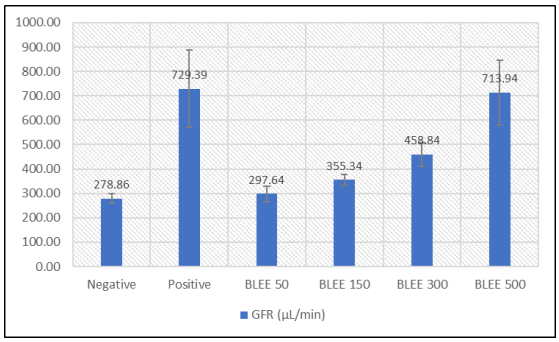

Figure 3 Comparison of eGFR across the groups

The estimated glomerular filtration rate (eGFR) was calculated using the formula from Besseling's study[19] for creatinine level ≥52 µmol/L, which is: $eGFR = 5682 \times W^{0.695} \times C^{-1.150} \times U^{-0.391}$, W is the weight of the rats in grams, C is creatinine level in µmol/L, and U is urea level in mmol/L. From the aforementioned formula, the highest eGFR was found in the positive control group (729.39 µL/min; SD:158.27 µL/min), followed by the BLEE 500 (713.94 µL/min; SD:132.51 µL/min). Meanwhile, the lowest eGFR was found in the negative control group (278.86 µL/min; SD:19.12 µL/min). Since the eGFR data was not distributed normally, analysis was conducted using Kruskall-Wallis and found a difference among all the groups ($p<0.001$). Further pairwise comparison it was found that there is a significant difference between the negative control group and the positive control group ($p<0.001$), BLEE 300 ($p<0.05$), and 500 group ($p<0.001$), and in comparison, with positive control group there is no significant difference with BLEE 300 and 500 group ($p>0.05$).

Despite some pathologic findings in several histopathological studies, all groups had no significant difference ($p>0.05$).

DISCUSSION

Bidara (*Z. mauritiana* Lam.), also known as Indian jujube, ber, or Malay jujube, is a plant from the Rhamnaceae family that has an important role in medicine, both traditional and modern, which is derived from the various bioactive compounds it contains, in its leaves, fruit, bark, and roots.[20–22] Bidara can grow as a shrub with a height of 1.2 to 1.8 meters or as a tree with a height of up to 12 meters, with dangling branches and zigzag twigs, and can be with or without thorns.[23] Bidara has leaves that change shape from elliptical-ovate or elliptical-oblong with a length of 2.5-6.25 cm and a width of 2-4 cm with whitish or brownish "hairs" on the underside of the leaf.[9,23] Bidara is native to Southeast and South Asia and has now spread to Africa, the Middle East, and China.

In this study, phytochemical screening of ethanol extract of Bidara (Z. mauritiana Lam.) leaves found alkaloid, saponin, flavonoid, tannin, and glycoside compounds. These findings are supported by the findings of Jha and Parihar (2024), who found that ethanol extract of Bidara (*Z. mauritiana* Lam.) leaves qualitatively contains carbohydrates, proteins, amino acids, steroids, glycosides, phytosterols, flavonoids, phenolic compounds and tannins, alkaloids, acidic compounds, and organic acids.[24] Other studies have also found that Bidara plants generally have various other phytochemical compounds, with terpenoid compounds being the most abundant.[6,9,32–35,24–31]

In these in-vivo experiments, BLEE showed antihyperglycemic effects at certain doses. This experiment shows that the antihyperglycemic effect of the BLEE is inextricably linked to the length of time the BLEE is used. This link is demonstrated by the decrease in the blood glucose levels in all experimental subject groups. From the induction of alloxan until the ninth day, the positive control and all BLEE groups did not have better antihyperglycemic performance than the negative control. The BLEE 300 and 500 group took effect more quickly as an antihyperglycemic with the same performance as the positive control (21 days), while the BLEE 150 took a little longer (24 days). These results are supported by previous studies that found that Bidara (*Z. mauritiana* Lam.) leaf extract has antihyperglycemic effects.[9,27,30–32,36,37] Several other experimental studies have also found that Bidara (*Z. mauritiana* Lam.) extract derived from either leaves, fruit, or seeds has antihyperglycemic effects in alloxan-induced hyperglycemic rats.[6,30] In the ethanol extract of Bidara (*Z. mauritiana* Lam.) seeds, the effective dose is 100 mg/kgBW; in the leaf extract, the effective dose is 300 mg/kgBW; while in the fruit extract, the effective dose is 400 mg/kgBW.[6,30] Another study found that saponin compounds isolated from Bidara (*Z. mauritiana* Lam.) leaves have an inhibitory effect on the enzyme α-amylase and have the potential to have an antihyperglycemic effect.[5] Other research proposes that the antihyperglycemic effect of Bidara (*Z. mauritiana* Lam.) was due to the inhibition activity against the enzymes α-amylase and α-glucosidase.[38] Meanwhile, another research in 2021 found that Bidara (*Z. mauritiana* Lam.) has a hypoglycemic effect that is directly proportional to the dose and has the same effectiveness as glibenclamide.[36]

This study specifically focuses on assessing the toxicity effect of Bidara (*Z. mauritiana* Lam.) leaf ethanol extract on the kidneys (nephrotoxicity) at therapeutic doses. The nephrotoxicity effect was assessed based on the serum urea and creatinine levels and the experimental subjects estimated glomerular filtration rate (eGFR). In addition, a histopathological examination of the kidney tissue was also conducted. There were no signs of nephrotoxicity in the experimental subjects that received BLEE, regardless of the dosage administered in this study. On the contrary, BLEE showed a nephroprotective effect at the given dose. This nephroprotective effect was indicated by the improvement in urea and creatinine levels and the increase in the eGFR of the test animals as the dose of BLEE increased. Research by Akanda and Hasan (2021) found that Bidara (*Z. mauritiana* Lam.) seed and bark extract showed no acute toxicity signs with doses of up to 4000 mg/kgBW. Hence, this study's 500 mg/kgBW dose can be categorized as safe.[36] Another study in 2023 found that in in-vitro experiments using the Brine Shrimp Lethality Test (BSLT) method, ethanol extract of Bidara (*Z. mauritiana* Lam.) leaves is toxic.[39] However, in an in-vivo study within the same report, with the same extract fraction at doses of 300 mg/kgBW and 500 mg/kgBW in Wistar rats, BLEE was no more toxic than the negative control.[39] This also supports Owolarafe and Kailani's previous study using Bidara (*Z. mauritiana* Lam.) leaves aqueous extract, which found that at a dose of 5000 mg/kgBB, Bidara leaves have no acute toxicity.[33] Another study on different species of Ziziphus, *Z. spina-christi*, also found no signs of acute toxicity to the kidneys or liver in experimental subjects, given the extract with either ethanol or aqueous solvent up to a dose of 2000 mg/kgBW.[40] However, different results were found in 2022 where methanol extract of Bidara root (*Z. mauritiana* Lam.) at high doses (500 and 1000 mg/kgBB) tended to be toxic with an LD50 of 375 mg/kgBB.[41] However, it should be emphasized that the latter experiment used different parts of Bidara (*Z. mauritiana* Lam.) plants (root) and different solvents (methanol), whilst this experiment used the leaves with ethanol solvent.

In the histopathological study of the experiment subject's kidneys, although some pathological features were seen in some experiment subjects, no signs of nephrotoxic effects were found in the subject's kidney tissue. These findings align with the study in 2022, which found no significant differences in the renal tissue profile between test animals that received ethanol extract of Bidara (*Z. mauritiana* Lam.) leaves with controls.[33]

CONCLUSION

According to the findings in this study, it can be concluded that Bidara (Z. mauritiana Lam.) leaves ethanol extract is a good antihyperglycemic agent and has no nephrotoxicity effect; on the contrary, it is nephroprotective.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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